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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,191	02/27/2007	Shuibing Chen	014740-001020US	4061

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,191	CHEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-19-10 has been entered.

Applicant's amendment filed 4-19-10 has been entered. Claims 20 has been amended. Claims 20-27 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 20-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using reversine (compound A) to induce dedifferentiation of murine C2C12 myoblast into multipotent stem cell losing myogenic specific markers MyoD and myosin, and differentiation of said multipotent stem cells into osteoblasts and adipocytes by using ODM and ADM, respectively, does not reasonably provide enablement for dedifferentiating various mesenchymal lineage committed mammalian cells into various or unknown multipotent stem cells, and said multipotent stem cells can differentiated into any cell type. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 20-27 are directed to a method of identifying compounds that induce dedifferentiation of mesenchymal linage committed mammalian cells into multipotent stem cells comprising culturing the mesenchymal lineage committed mammalian cells with a test compound, which is elected Formula 1 species from 2,6-disubstituted purines, culturing said cells in a first cell differentiation culture media that induces differentiation of the multipotent stem cell into a first cell type, and culturing said cells in a second cell differentiation culture media that induces differentiation of the multipotent stem cell into a second cell type, wherein

induction of differentiation into both first and second cell types identifies the test compound as a dedifferentiation compound. Claim 21 specifies the first cell culture medium induces osteogenesis and the second culture medium induces adipogenesis, wherein the first cell type is an osteoblast and the second cell type is an adipocyte. Claims 24 and 25 specify induction of osteogenesis is detected by expression of an osteogenesis marker gene and induction of adipogenesis is detected by expression of an adipogenesis marker gene, respectively. Claims 26 and 27 specify the marker gene for osteogenesis and adipogenesis, respectively.

The specification discloses that murine C2C12 cell is a myogenic lineage committed myoblast, exposure of C2C12 cells to a 2-(4-morpholinoanilino-6-cyclohexylamino-purine analog (compound A or reversine, Figure 2) induces high level (7 fold) of alkaline phosphatase (ALP) activity relative to the DMSO control treatment. Reversine inhibits myotube formation and myogenic specific marker such as MyoD and myosin begin to disappear. After 4 days of treatment with reversin, the compound was removed and cells were grown in osteogenic differentiation medium (ODM) or adipogenic differentiation medium (ADM), and 35% of cells stained positive for ALP and 40% of cells had the characteristic fat cell morphology and stained positive for Oil Red O, respectively (e.g. Examples 3 and 4). The claims encompass inducing dedifferentiation of various mesenchymal lineage committed mammalian cell to multipotent stem cell, identification of the multipotent stem cell, differentiation of said multipotent stem cell into various cell types and identification of said cell types. The mesenchymal lineage committed mammalian cells include osteoblasts (bone cells), chodrocytes (cartilage cells), adipocytes (fat cells), myocytes (muscle cells), hematopoietic cells, fibroblasts, stromal or tendon cells, and cells of connective tissues etc., and the cell can be derived from numerous different mammals, such as

mice, rats, other rodents, humans, monkey, baboons, chimpanzee, other primates, horse, cows, pigs, sheep, dogs, cats, whales, and other mammals etc.

The specification fails to provide adequate guidance and evidence for whether and how the osteoblasts, chondrocytes, adipocytes, myocytes (muscle cells), hematopoietic cells, fibroblasts, stromal or tendon cells, and cells of connective tissues can be dedifferentiated by a test compound into multipotent stem cells and said multipotent stem cells can be induced into particular cell type such that the test compound can be identified as a compound that induces dedifferentiation of lineage committed mammalian cells. The specification only discloses that myoblasts can be dedifferentiated by reversine into multipotent stem cells that can be differentiated into osteoblasts and adipocytes. The cited reference Saraiya in the amendment filed 4-19-10 (Exhibit B) discloses treatment of human annulus fibrosus cells with reversine induces the cells to become multipotent stem cells that can differentiate into otsteogenic cells, adipogenic cells and chondrogenic cells. It appears that the human annulus fibrosus cells are a type of muscle cells (myoblasts). The dermal fibroblasts used in the cited reference Fania (Exhibit C) appears to be the fibroblast cells of the elastic fibers in the dermis and the dermal fibroblast could be a muscle cells. It seems that the state of the art of dedifferentiation of mesenchymal lineage committed mammalian cells only shows dedifferentiation of muscle cells by reversine into multipotent stem cells that can be differentiated into osteoblasts, adipocyte, or chondrocytes. There is a lack of information and guidance for whether and how the osteoblasts, chondrocytes, adipocytes, myocytes (muscle cells), hematopoietic cells, fibroblasts, stromal or tendon cells, and cells of connective tissues can be dedifferentiated by a test compound into multipotent stem cells and said multipotent stem cells can be induced into particular cell type

such that the test compound can be identified as a compound that induces dedifferentiation of lineage committed mammalian cells. The claims only require exposing a test compound to the mesenchymal lineage committed mammalian cells but are silent about whether multipotent stem cells are generated or not and what kind of multipotent stem cells are generated. If there are no multipotent stem cells generated, then, there is no "dedifferentiation" of the mesenchymal lineage committed mammalian cells and it could be "transdifferentiation" of the mesehnchymal linage committed mammalian cells into the first and second cell types. Therefore, the test compound can not be identified as a compound that induces "dedifferentiation" or can be mistaken as a compound that induces "dedifferentiation" of linage committed mammalian cells. Further, the first and second cell type can be any cell type and can be the same cell type. When the first and second cell types are the same as the initial mesenchymal lineage committed mammalian cells and it is unclear whether there are multipotent stem cells generated or not, it is unclear how to identify the test compound as a compound that induces dedifferentiation of lineage committed mammalian cells.

The specification also fails to provide adequate guidance and evidence for what kind of multipotent stem cells can be obtained from dedifferentiation of various mesenchymal lineage committed mammalian cells derived from numerous different mammals, and how to identify numerous different cell types differentiated from said multipotent stem cells derived from various mammals.

The cell markers for multipotent stem cells and for differentiated mammalian cells differ among different cell types and different mammalian species. There are dramatic molecular and cellular differences between human and mouse embryonic stem cells. Allegrucci et al., 2006

(Human Reproduction Update, Vol. Advance Access published on August 26, 2006, p. 1-18) demonstrates that there is difference in pluripotency marker molecules, transcriptional profiling, genetic stability and epigenetic stability even among different human embryonic stem cell lines (e.g. abstract). There are differential expression of different markers among different human ES cell lines and "[t]he physiological significance of expression of these markers is not clear, and it is likely that the limited panel of markers in current use may be insufficient to define the state of 'stemness' because many of them are not unique to embryonic stem cells" (e.g. p. 2, right column). Sato et al., 2003 (Developmental Biology, Vol. 260, p. 404-413) shows that there are 918 different gene expressions between human embryonic stem cell line H1 (HESC H1 line) and mouse embryonic stem cells (MESCs) (e.g. Figure 4A). There are molecular markers that are unique for HESCs as compared to MESCs, for example, SOCS-1, an inhibitor of the STAT-3 signaling pathway, is enriched in HESCs but not in MESCs (e.g. p. 412, left column, 3rd paragraph). Sato also suggests that different human ES lines have different transcriptional profiles and respond differently to the differentiation conditions (e.g. p. 412, left column, last paragraph). Rao, M., 2004 (Developmental Biology, Vol. 275, p. 269-286) reports some known differences between mice and human ES cells (e.g. table 3). The difference between mice and human ES cells is much higher than that seen in human-to-human cell comparison (e.g. p. 282, left column, 1st paragraph). Indeed, there are different molecular markers even among different human ES cells. Abeyta et al., 2004 (Human Molecular Genetics, Vol. 13, No. 6, p. 601-608) compares gene expression profiles of different human ES cell lines, HSF-1, HSF-6 and H9 lines. Abeyta observed that each line has a unique expression signature and the expression of many genes was limited to just one or two hESC lines. Abeyta suggests that "the observed differences

in gene expression between independently-derived hESC lines may reflect inherent differences in the initial culture of each line and/or the underlying genetics of the embryos from which the lines were derived" (e.g. abstract). It appears that human, rat and mouse ES cells could have different specific cell markers (human and mice have dramatically different expression profiles) and the cell markers could be different even among different human ES cells, and there are differential expressions even among common cell markers. Differences in gene expression between independently-derived hESC lines may reflect inherent differences in the initial culture of each line and/or the underlying genetics of the embryos from which the lines were derived, and they can respond differently to the differentiation conditions.

Similarly, the expression profiles among human, rat and mice hair follicle stem cells could differ dramatically. Yu et al., 2006 (American Journal of Pathology, Vol. 168, No. 6, p. 1-6) points out that human hair follicle-derived stem cells are not able to proliferate using the medium condition as disclosed by the prior art and suggests different biological behaviour of mouse and human stem cells and further points out that "[n]estin is a marker for neural progenitor cells" (e.g. p. 8, left column). Cotsarelis, G., 2006 (The Journal of Clinical Investigation, Vol. 116, No. 1, p. 19-22) reports that there are differences between mouse and human hair follicle stem cell markers, "[I]n particular, CD34, which delineates hair follicle stem cells in mouse, is not expressed by human hair follicle stem cells, while CD200 is expressed by stem cells in both species" (e.g. abstract). There are other genes that are expressed in human hair follicle stem cells but not expressed in mouse hair follicle stem cells, including PHLDA1, FOLLISTATIN and DI02 (e.g. Table 1). Cotsarelis further points out that "the cellular and molecular characteristics of stem cells in the human follicle could be quite different from those

in the rodent" (e.g. p. 20, right column). It appears that human, rat and mouse hair follicle stem cells could have different specific cell markers and it is unclear what would be the cell marker for the human and rat hair follicle stem cells. It was unpredictable what would be the cell markers for various different human, rat and mouse hair follicle stem cells. It was known in the art that a stem cell expresses various different specific cell markers, which specifically defines said stem cells. It is apparent that cell markers to identify multipotent stem cells or differentiated mesenchymal lineage committed mammalian cells vary among different multipotent stem cells and among different differentiated cells from different mammalian species, and even vary among different cell lines. The specification only discloses cell markers for the identification of osteoblasts and adipocytes but fails to provide adequate guidance for how to identify the vast number of multipotent stem cells, various cell types, and cells derived from tens of thousands of different mammalian species. Absent specific guidance, one skilled in the art at the time of the invention would not know how to identify compounds that induce dedifferentiation of various lineage committed mammalian cells into numerous different multipotent stem cells.

The claims encompass using numerous different test compounds but the specification fails to provide adequate guidance and evidence for what kind of multipotent stem cells can be induced by those various test compounds. The test compounds have diverse functions and effects on different mammalian cell types and it is unclear what kind of multipotent stem cells can be induced from various mesenchymal lineage committed mammalian cells derived from numerous different mammalian species. There is also a lack of correlation between the lineage committed mammalian cells and the differentiated first and second cell type so as to determine that the test compound is indeed a compound that induce dedifferentiation of lineage committed

mammalian cells. The differentiated first and second cell types must be lineage correlated to the mesenchymal lineage committed mammalian cells exposed to the test compound such that differentiation of a multipotent stem cell into both first and second cell types could be used as an indicator that said test compound is a compound that induces dedifferentiation of lineage committed mammalian cells. Absent specific guidance, one skilled in the art at the time of the invention would not know how to practice the claimed invention.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of one of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicant argues that the claims have been amended to recite dedifferentiation of mesenchymal lineage committed mammalian cells into multipotent stem cells. Applicant cites reference Jaenisch and argues that there are various cells having different developmental potency, ranging from totipotent cells, pluripotent cells, multipotent cells, unipotent cells, and lineage committed and differentiated cells. One skilled in the art would appreciate that the multipotent stem cells can be determined by testing whether such cells can be induced to differentiate into more than one type of mesenchyal lineage committed cell type. The specification shows that murine myoblast cells, C2C12 cells, can be dedifferentiated by reversine and the dedifferentiated cells can be differentiated into both osteogenic cells and adipogenic

cells. Applicant further cites reference Saraiya and reference Fania and argues that human annulus fibrosus cells and murine fibrobalsts can be dedifferentiated to multipotent cells by reversine and said multipotent cell can differentiate into osteogenic cells, adipogenic cells and chondrogenic cells (amendment, p. 4-7). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112, first paragraph, rejection.

Applicant argues that one skilled in the art would know how to identify numerous mesenchymal lineage committed cell types across various mammalian species by using routine histological and morphological criteria and the phenotypic characteristics of the various mesenchymal lineage committed cell types are evolutionary conserved across mammalian. One skilled in the art can identify mesenchymal lineage committed mammalian cells without undue experimentation (amendment, p. 7-8). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112, first paragraph, rejection. The specification fails to provide adequate guidance and evidence for whether and how the osteoblasts, chondrocytes, adipocytes, myocytes (muscle cells), hematopoietic cells, fibroblasts, stromal or tendon cells, and cells of connective tissues can be dedifferentiated by a test compound into multipotent stem cells and said multipotent stem cells can be induced into particular cell type such that the test compound can be identified as a compound that induces dedifferentiation of lineage committed mammalian cells. The claims only require exposing a test compound to the mesenchymal lineage committed mammalian cells but are silent about whether multipotent stem cells are generated or not and what kind of multipotent stem cells are generated. If there are no multipotent stem cells generated, then, there is no “dedifferentiation" of the mesenchymal lineage committed mammalian cells and it could be “transdifferentiation” of the mesehnchymal linage committed

mammalian cells into the first and second cell types. Therefore, the test compound can not be identified as a compound that induces "dedifferentiation" or can be mistaken as a compound that induces "dedifferentiation" of linage committed mammalian cells. It is unclear what kind of multipotent cells could be generated and how to identify those multipotent cells by specific cell markers. There is also a lack of correlation between the lineage committed mammalian cells and the differentiated first and second cell type so as to determine that the test compound is indeed a compound that induce dedifferentiation of lineage committed mammalian cells. The differentiated first and second cell types must be lineage correlated to the mesenchymal lineage committed mammalian cells exposed to the test compound such that differentiation of a multipotent stem cell into both first and second cell types could be used as an indicator that said test compound is a compound that induces dedifferentiation of lineage committed mammalian cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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